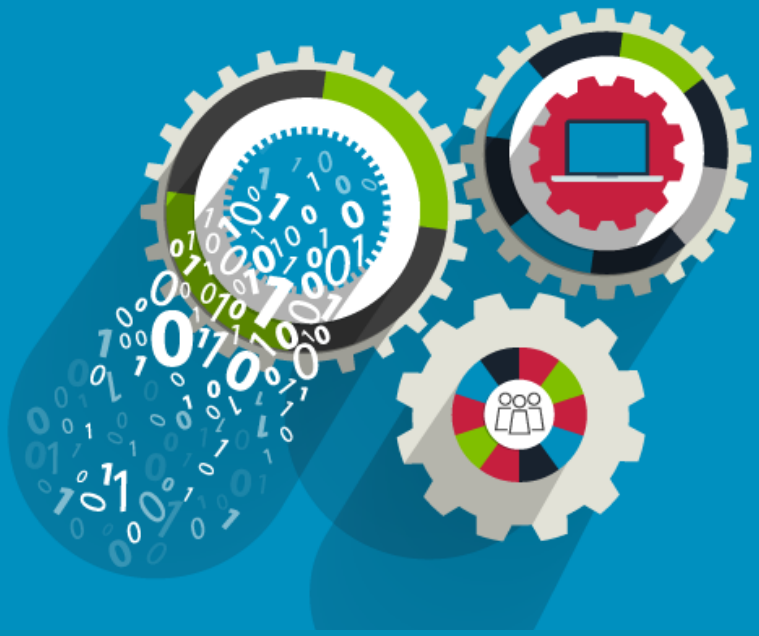

# Domain-specific Design of Patient Classification in Cancer-related Cachexia Research


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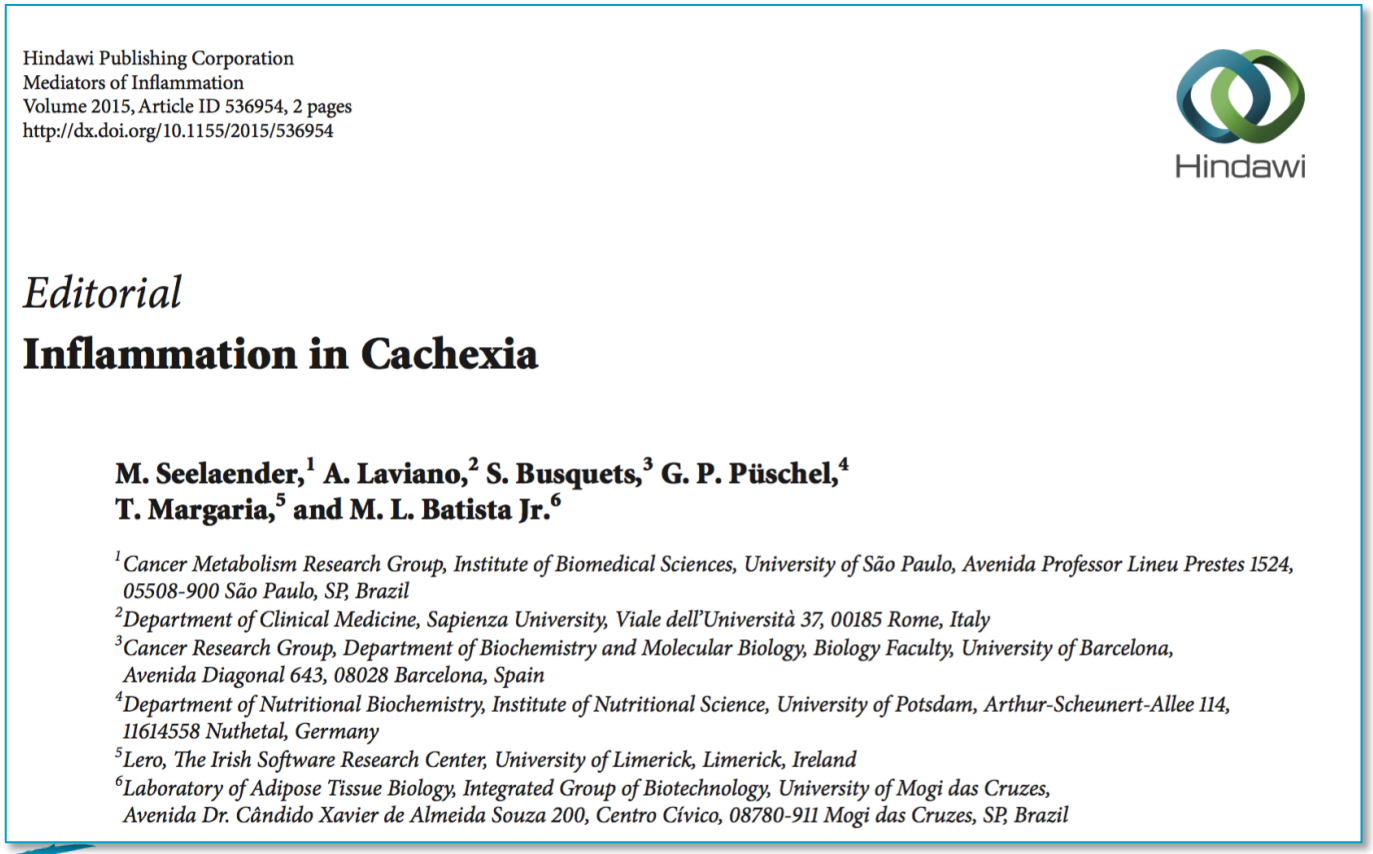
# Motivation

Cachexia is a **complex wasting syndrome** associated with a marked detrimental effect upon life quality and survival in patients with **cancer**, **chronic obstructive pulmonary disease** (COPD), **chronic heart failure**, **AIDS**, and **chronic kidney disease**, among other conditions. Its prevalence is of around 5 to 15% in cardiac patients at end stage, rising up to 30%, in COPD and chronic kidney disease patients, and to **80% in patients with advanced cancer**. Cachexia symptoms include **pronounced weight loss**, due to both lean and fat mass wasting: **anorexia, malabsorption, nausea, asthenia, neuroendocrine changes, immune system function impairment, and disruption of energy metabolism**.

Despite its unquestionable relevance to the poorer outcome of treatment in disease and its high prevalence among patients, the syndrome is **still underdiagnosed and seldom treated**. Part of the difficulty in treating cachexia relies on the fact that, in the clinical setting, the syndrome is recognised solely in its **most advanced stages**, when therapy available to the present day is not able to fully reverse its symptoms.

# Motivation

Therefore, scientists and clinicians should focus on **identifying early changes**, as to intervene in a precocious manner. Taken together, the issue provides insights on the importance of **detecting early signs of inflammatory changes** in patients and examines the **mechanisms that act in concert**, inducing cachexia symptoms.



Hindawi Publishing Corporation
Mediators of Inflammation
Volume 2015, Article ID 536954, 2 pages
http://dx.doi.org/10.1155/2015/536954

Hindawi

*Editorial*

**Inflammation in Cachexia**

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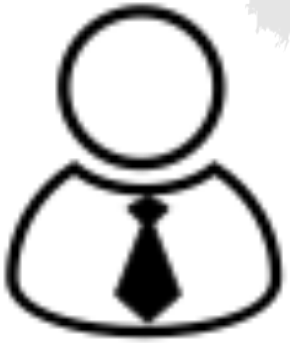
[6]*Laboratory of Adipose Tissue Biology, Integrated Group of Biotechnology, University of Mogi das Cruzes, Avenida Dr. Cândido Xavier de Almeida Souza 200, Centro Cívico, 08780-911 Mogi das Cruzes, SP, Brazil*

# External Groups

**Table 1.** Remote associated groups and their geographical location and affiliation.

| Group | Institute/Country |
|---|---|
| Alessandro Laviano, Maurizio Muscaritoli | Department of Clinical Medicine Sapienza University of Rome, Rome, Italy. |
| Giorgio Trinchieri, Romina Goldzmid | Center for Cancer Research National Cancer Institute, Bethesda, Maryland USA |
| Josep M. Argilés, Silvia Busquets | Cancer Research Group, Institut de Biomedicina, Univ. Barcelona Barcelona, Spain |
| Nicolaas Deutz | Department of Health & Kinesiology Texas A&M University Bryan, Texas, USA |
| Stephen Farmer | Department of Biochemistry Boston University School of Medicine Boston, MA, USA |
| Gerhard Paul Püschel | Institute of Nutritional Science University of Potsdam Potsdam, Germany |
| *Tiziana Margaria* | *Institute of Informatics University of Potsdam Potsdam, Germany* |
| *Barry D. Floyd* | *California State Polytechnic University San Luis Obispo, CA, USA* |



Application Experts

Technical Experts

# Main Challenge

- Life sciences researchers are seldom IT professionals
  - they need  to **work together efficiently**
  - with the data definition and management techniques that **complex and evolving experimental settings** require

# Definition of Cachexia

## Cachexia: A new definition

William J. Evans*, John E. Morley [a], Josep Argilés [a], Connie Bales [a], Vickie Baracos [a], Denis Guttridge [a], Aminah Jatoi [a], Kamyar Kalantar-Zadeh [a], Herbert Lochs [a], Giovanni Mantovani [a], Daniel Marks [a], William E. Mitch [a], Maurizio Muscaritoli [a], Armine Najand [a], Piotr Ponikowski [a], Filippo Rossi Fanelli [a], Morrie Schambelan [a], Annemie Schols [a], Michael Schuster [a], David Thomas [a], Robert Wolfe [a], Stefan D. Anker [a]

### CACHEXIA DIAGNOSIS

Weight loss of at least 5% in 12 months or less

(or BMI <20 kg/m$^2$)

3 of 5

- Decreased muscle strength
- Fatigue
- Anorexia
- Low fat-free mass index
- Abnormal biochemistry:
  - Increased inflammatory markers (CRP, IL-6)
  - Anemia (Hb <12 g/dL)
  - Low serum albumin (<3.2 g/dL)

# What data do we have?

- Questionnaire scores
- Anthropometric data
- Body composition images
- Brain images
- Histological images
- Immunodetection images
- Biochemical parameters in plasma
- Endocrine parameters in plasma
- Inflammatory parameters in plasma
- Biochemical parameters in tissues/organs
- Inflammatory parameters in tissues/organs
- Cell sorting and phenotyping spectra
- Chromatographic spectra
- Molecular parameters in cells
- Microarray analysis
- Gene sequencing
- Physiological parameters associated with the effect of exercise

# How to work with all these information?

- PDF Files
- Excel spreadsheets
- Everything is done manually

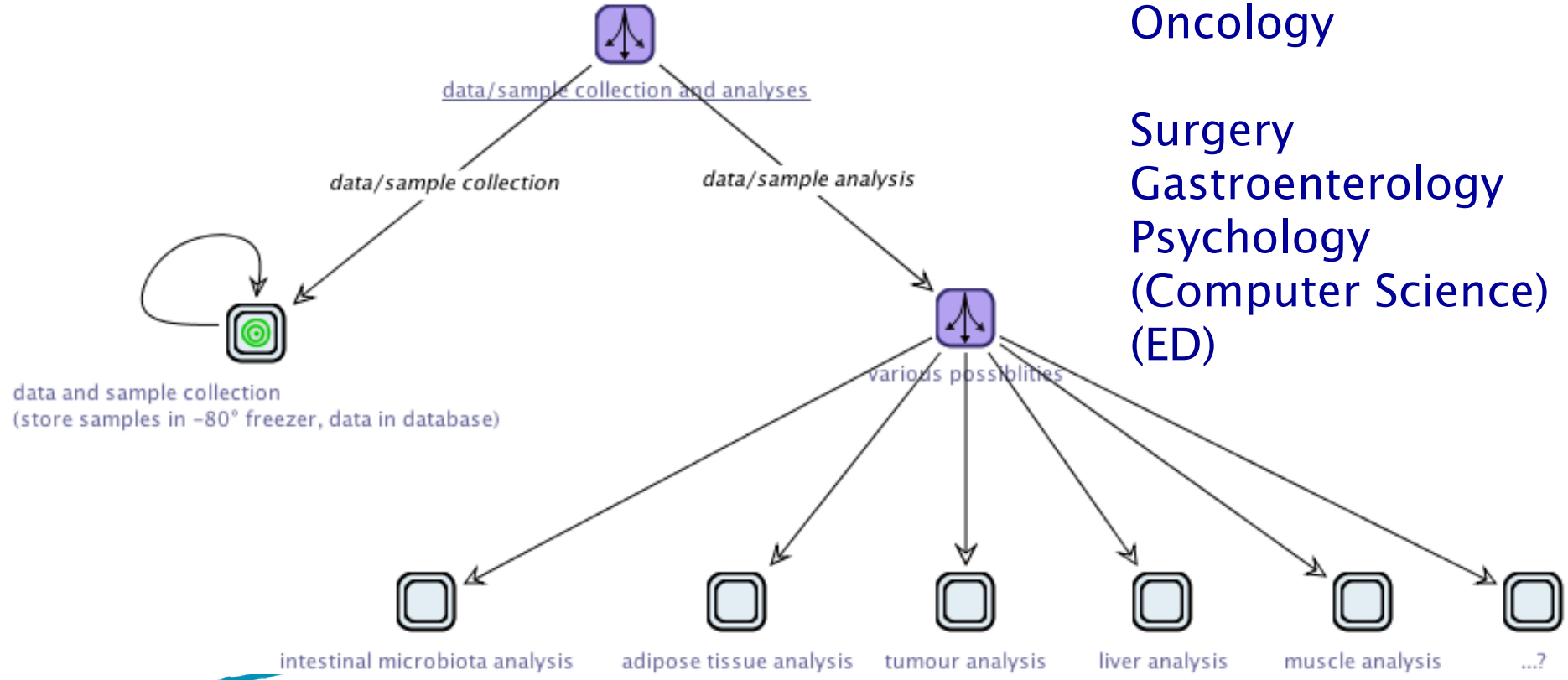
**Interdisciplinary:**
Bio-chem lab
Nutrition science
Immunology
Sports/rehab
Oncology

Surgery
Gastroenterology
Psychology
(Computer Science)
(ED)

**Managing Processes**

# Managing Processes

## Cachexia – the Big Picture
**(DAAD, FAPESP, CAPES)**




**Interdisciplinary:**
Bio-chem lab
Nutrition science
Immunology
Sports/rehab
Oncology

Surgery
Gastroenterology
Psychology
(Computer Science)
(ED)

# Stakeholder Requirements:

- semiotically **intuitive, graphical approach**
- a framework that:
  - is able to **manage complexity and change**
  - **helps** to **efficiently produce** more reliable **results**
  - appears **simple** and **intuitive** to its users

# The Patient Classification Spreadsheet

| | A | B | C | D | E | F | G |
|---|---|---|---|---|---|---|---|
| 1 | **PATIENT'S INFORMATION** | | | | **FIRST CRITERION - WEIGHT LOSS** | | |
| 2 | **Identification** | **Gender** | **Age (Years)** | | **Weight variation** | **BMI (kg/m²)** | **Result** |
| 3 | 165A | Male | 51 | | -10% | 28,88 | IN |
| 4 | **Height (m)** | **Prev. weight (kg)** | **Current weight (kg)** | | **Treatment** | Hernia | |
| 5 | 1,59 | 81 | 73 | | | | |
| 6 | | | | | | | |
| 7 | **SECOND CRITERION - WEIGHT STRENGTH** | | | | **THIRD CRITERION - FATIGUE** | | |
| 8 | **Method** | **Score** | **Result** | | **Method** | **Score** | **Result** |
| 9 | Questionnaire (QLC-C30) | 53,33333333 | OUT | | Questionnaire (QLC-C30) | 33,33 | IN |
| 10 | **Answer 1** | 1 | | | **Answer 10** | 4 | |
| 11 | **Answer 2** | 4 | | | **Answer 12** | 3 | |
| 12 | **Answer 3** | 2 | | | **Answer 18** | 2 | |
| 13 | **Answer 4** | 3 | | | | | |
| 14 | **Answer 5** | 2 | | | | | |
| 15 | | | | | | | |
| 16 | **FOURTH CRITERION - ANOREXIA** | | | | **FIFTH CRITERION - FAT FREE MASS INDEX** | | |
| 17 | **Method** | **Score** | **Result** | | **Method** | **Score** | **Result** |
| 18 | Questionnaire (QLC-C30) | 100,00 | OUT | | DEXA Scan | 6,09 | IN |
| 19 | **Answer 13** | 1 | | | **Lean mass (kg)** | 15,4 | |
| 20 | | | | | | | |
| 21 | | | | | | | |
| 22 | **SIXTH CRITERION - BIOCHEMICAL PARAMETERS** | | | | **GROUP CLASSIFICATION** | | **BARCODE** |
| 23 | **Parameters** | **Concentration** | **Result** | | CACHEXIA WITHOUT CANCER | | 165ACWCEXNONE |
| 24 | C-Reactive protein (mg/l) | 6,10 | IN | | **LEVEL OF EXCLUSION CRITERIA** | | |
| 25 | IL-6 (pg/ml) | 5,34 | | | 0 | NONE | |
| 26 | Anemia - Hb (g/dl) | 12,30 | | | | | |
| 27 | Albumin (g/dl) | 4,89 | | | | | |
| 28 | Adapted from Evans, 2008 | | | | | | |

# Example: Excel Formula (Cell B9)

```
=WENN(UND(A9="Questionnaire (QLC-C30)";B10<>"";B11<>"";
B12<>"";B13<>"";B14<>"");(1-(MITTELWERT(B10:B14)-1)/3)*100;
WENN(UND(A9="HandgripTest";B3="Male";B10<44;B10<>""); "POOR";
WENN(UND(A9="HandgripTest";B3="Male";B10>44; B10<>"");"GOOD";
WENN(UND (A9="HandgripTest"; B3="Female";B10<23;B10<>"");"POOR";
WENN(UND(A9="HandgripTest"; B3="Female";B10>22;B10<>"");
"GOOD";"---")))))
```

- for regular use in large-scale research projects it has significant **drawbacks**:
  - for every patient the **data** has to be **entered manually** in a single spreadsheet → also the result has to be **transferred manually**
  - Excel **formulas are complex** and not easily understandable
  - maintenance, modifications, and extensions are difficult and error-prone
  - **no statistics** on the data possible
  - **no unified database**

# The Patient Classification Spreadsheet

- complex **patient classification determines** which individuals belong to the different patient and control **groups**
- it is a **multifaceted evaluation** of a number of interdisciplinary **criteria**

We

- organized and simplified the patient classification process,
- made it **easily accessible** and **shareable** worldwide via a web application
- the integrated framework collects the data of patients in a **central repository** (easy to access and back up)

# Approach

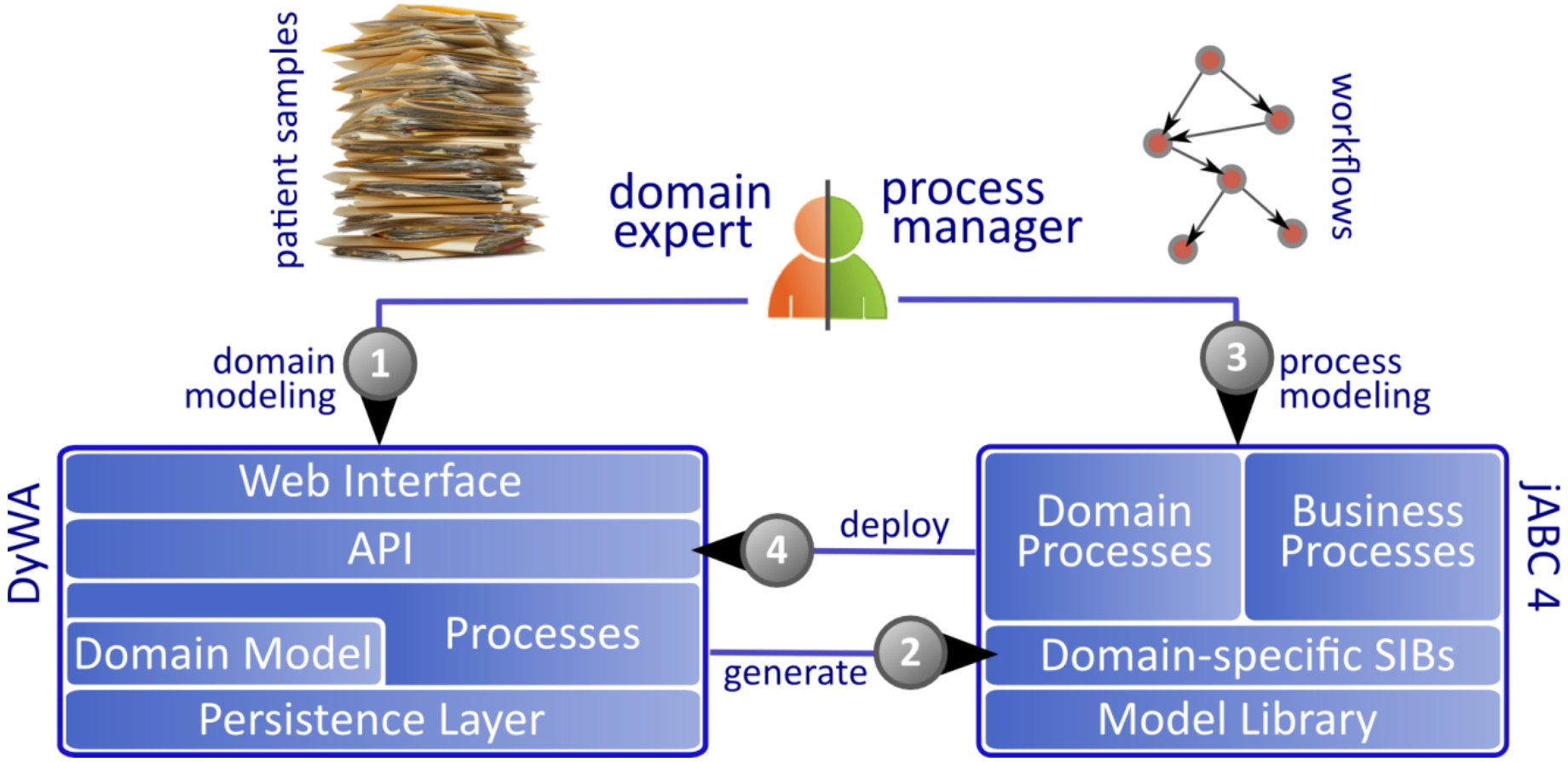
IDE for **co-design** and **co-evolution** of data and process models

- Data: Dynamic Web Application (**DyWA**),
- Behaviour: Java Application Building Center 4 (**jABC4**) modeling framework

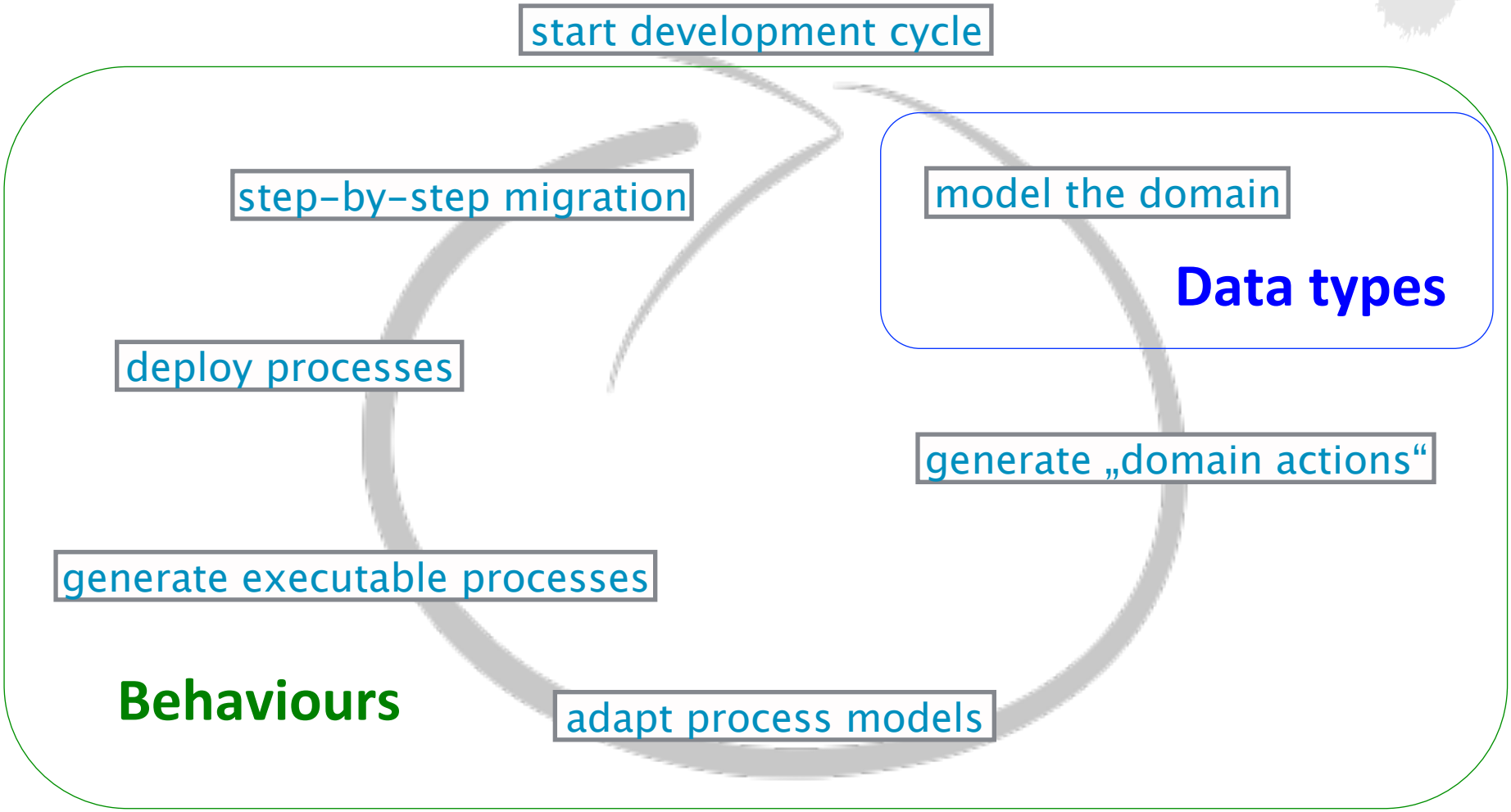
**Result**:

easily executable domain-specific processes

# Co-Development with DyWA and jABC4



# Prototype-Driven Development (DevOps style)

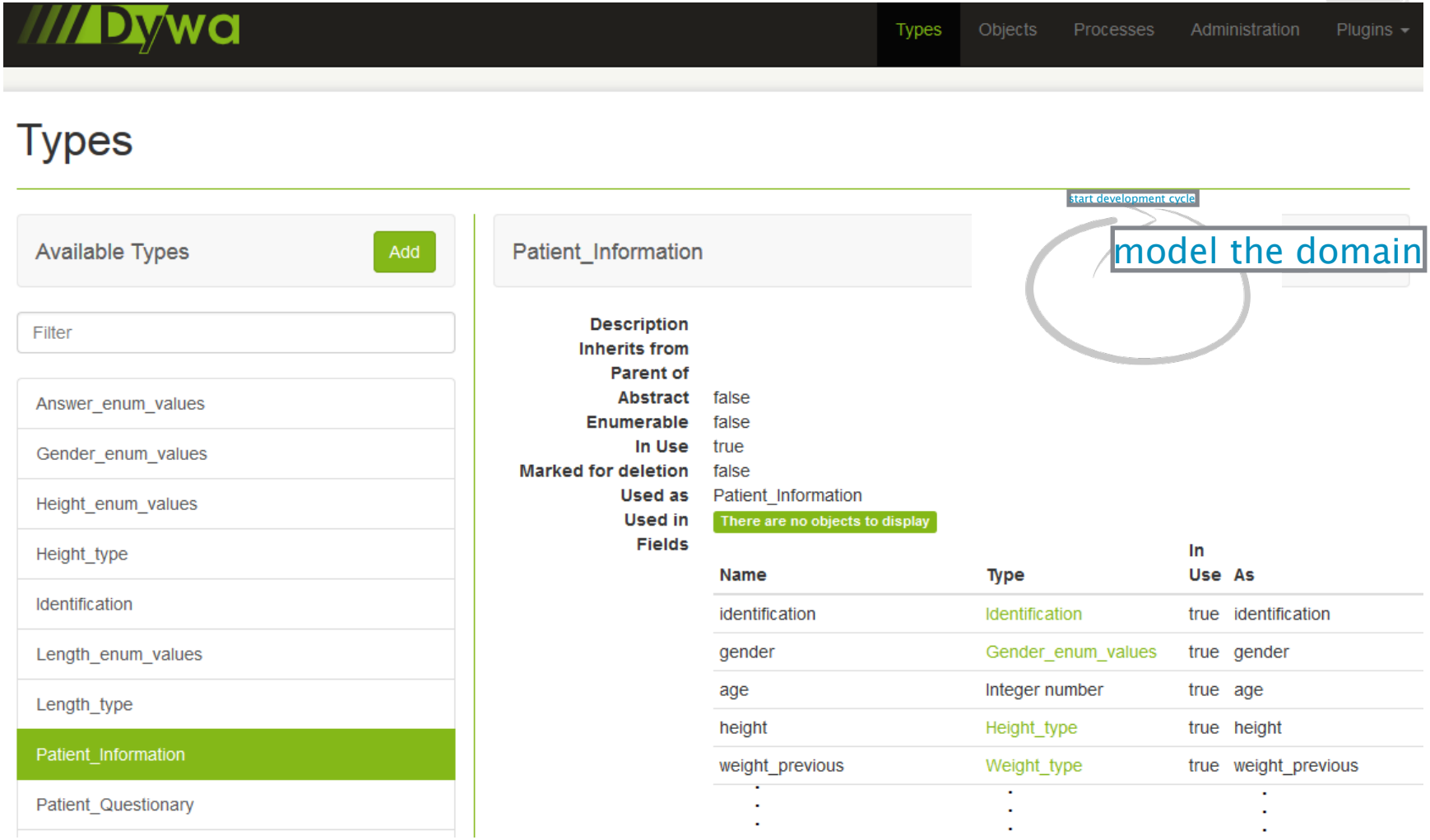


# DyWA: Data Type Definition

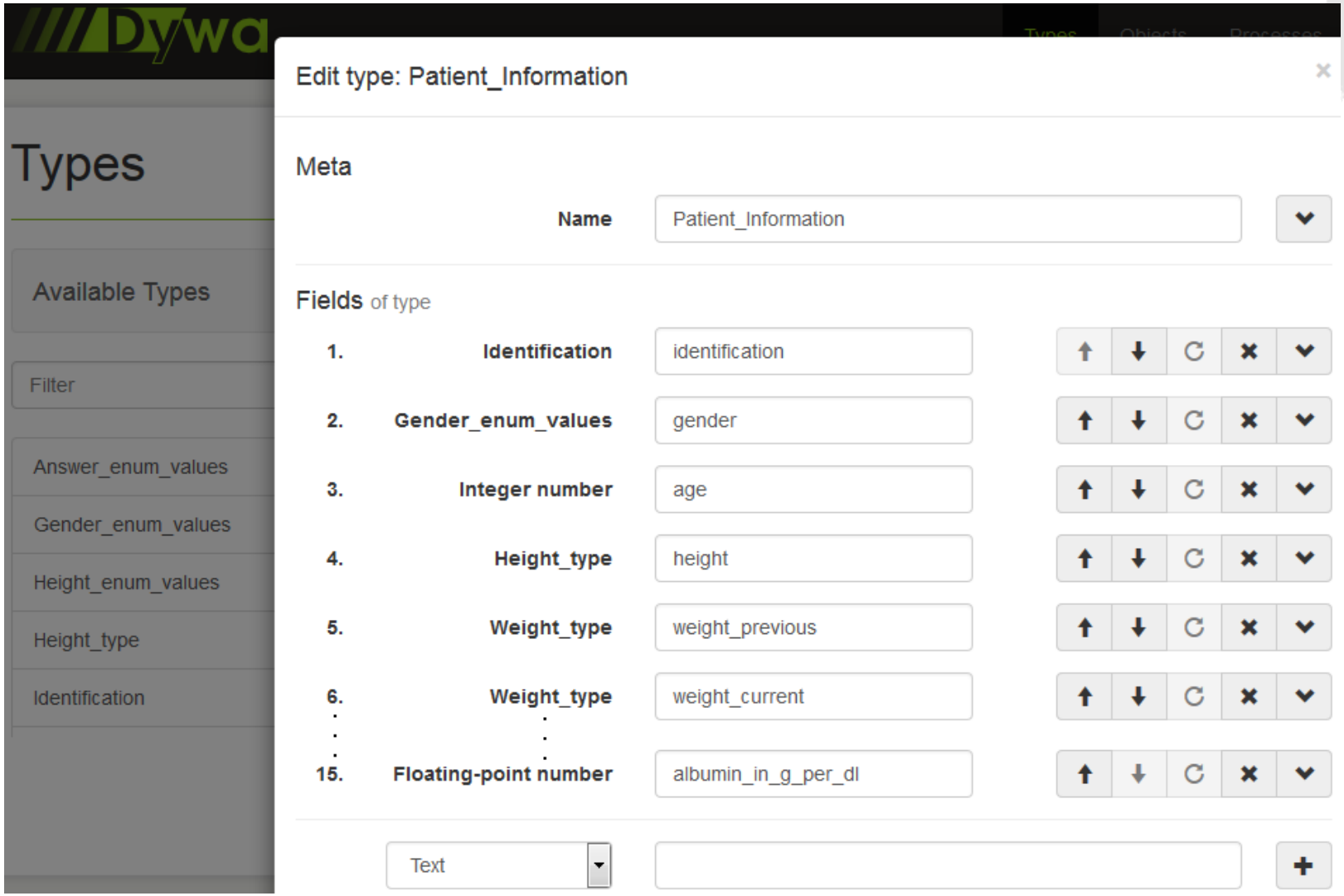
- DSL design approach = start by fixing the vocabulary of the domain
- definition of a set of domain-relevant "***things***" with their respective types
- DyWA provides **domain-independent** Java types (e.g. String, Integer) as initial type collection
- any **self-modeled** domain specific **type** (e.g. ***Weight***) becomes directly available and can be used as a field or attribute of complex data types
- **CRUD** operations = **C**reate, **R**ead, **U**pdate, **D**elete are automatically generated for every defined **type** and **field** by the DyWA

# DyWA: Data Type Definition

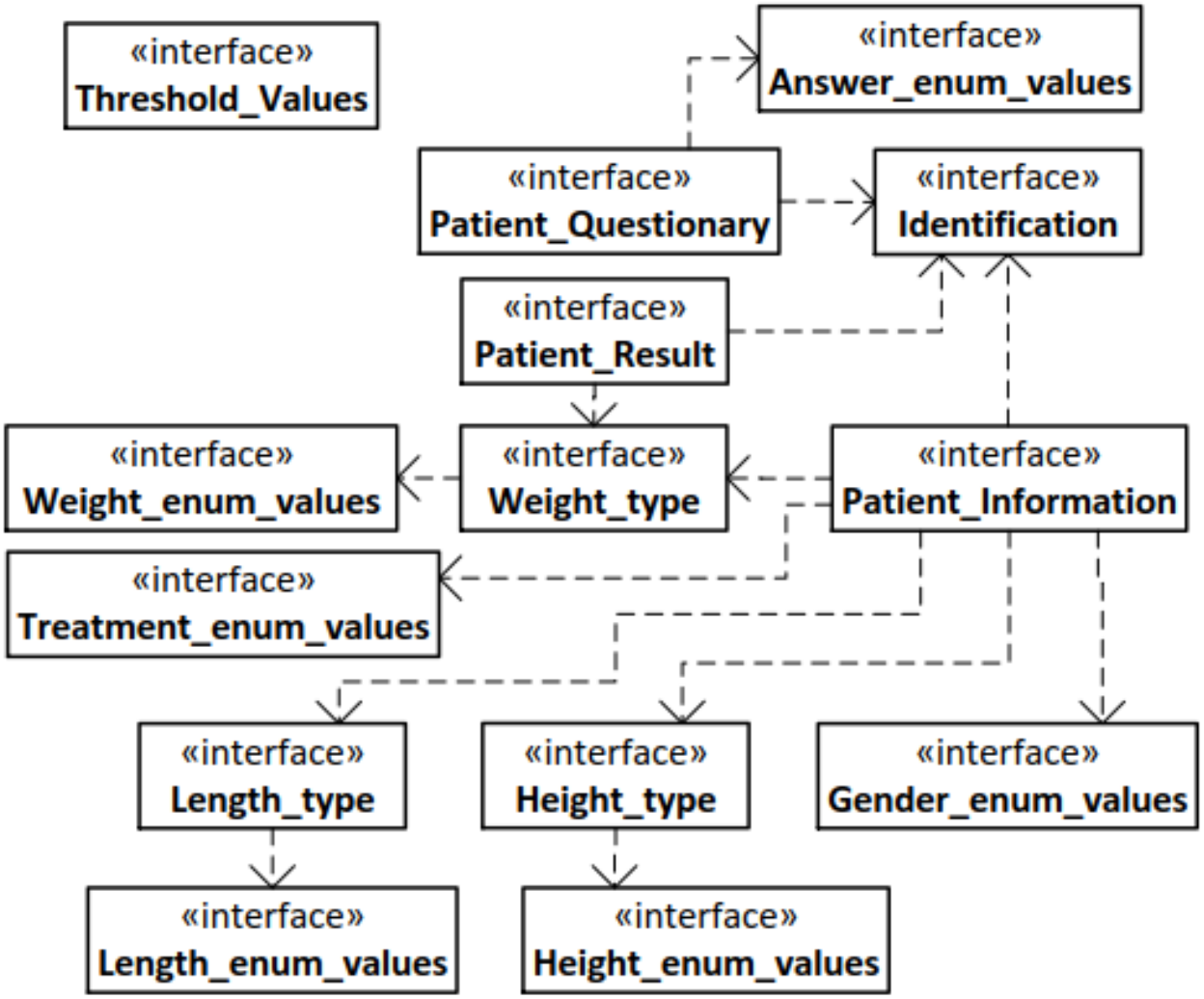
## (Margaret Hamilton: who you are)



# DyWA: Data Type Definition

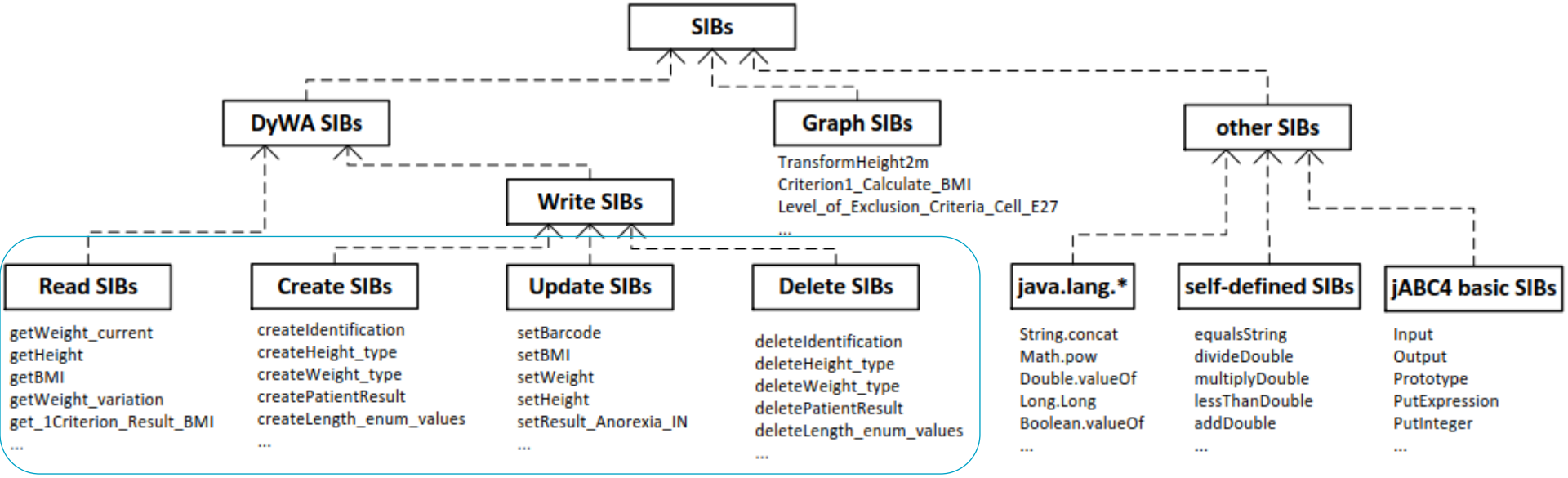


# UML Class Diagram of the Domain Model



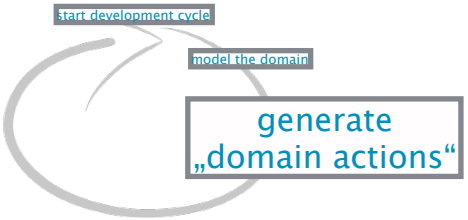
# Taxonomy of SIBs: the „Microservices“

## (Margaret Hamilton: what you do)

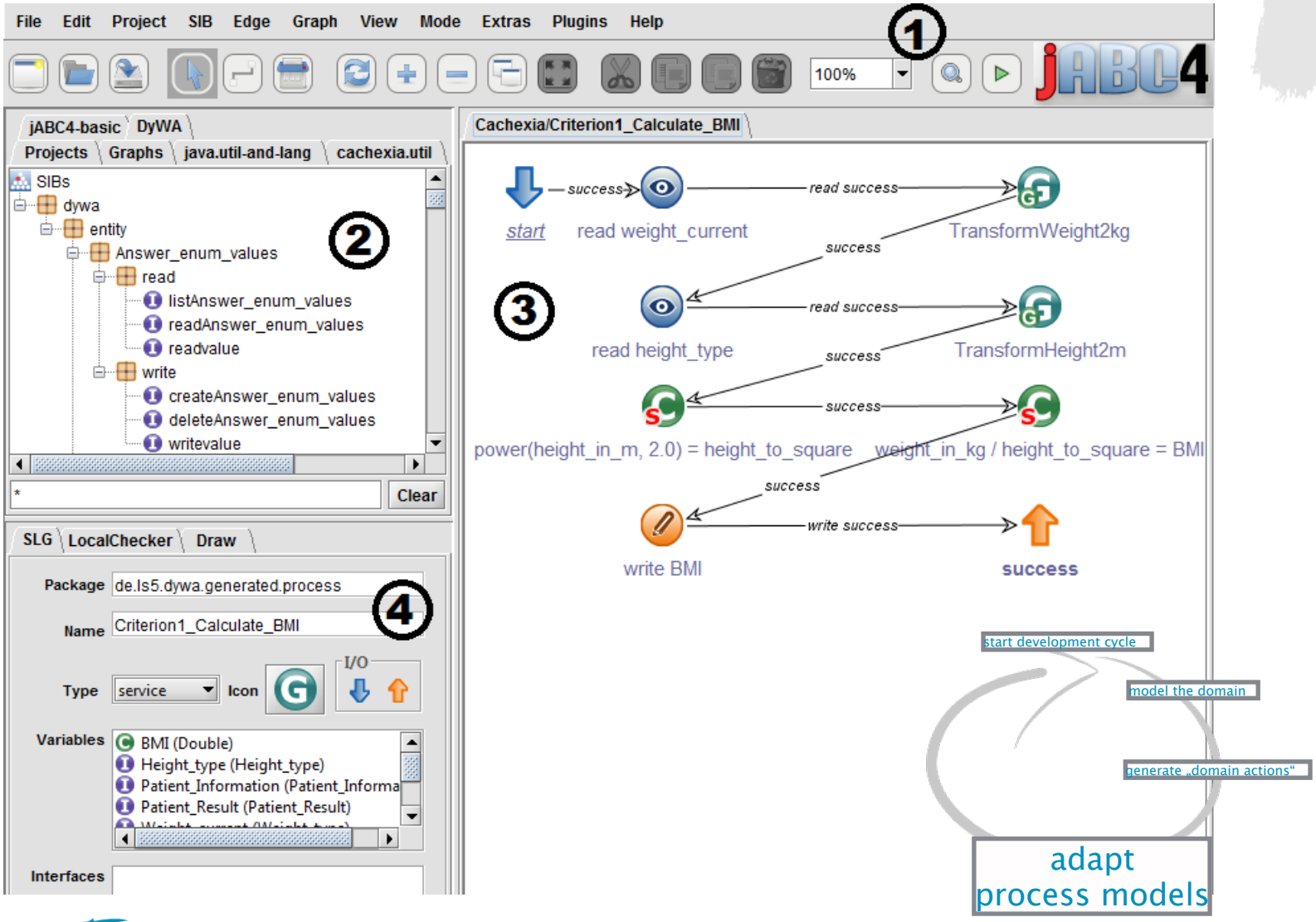



CRUD SIBs automatically generated

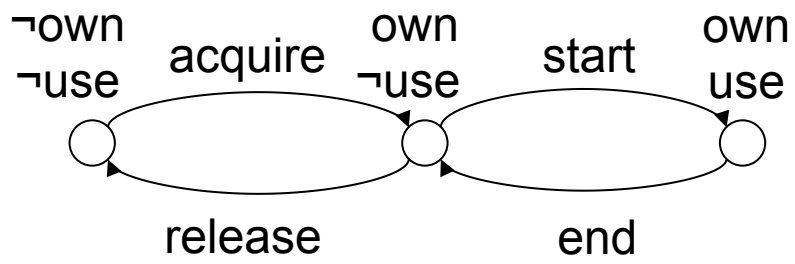
**“emerging” DSL for healtcare**



# Process Modeling with jABC4



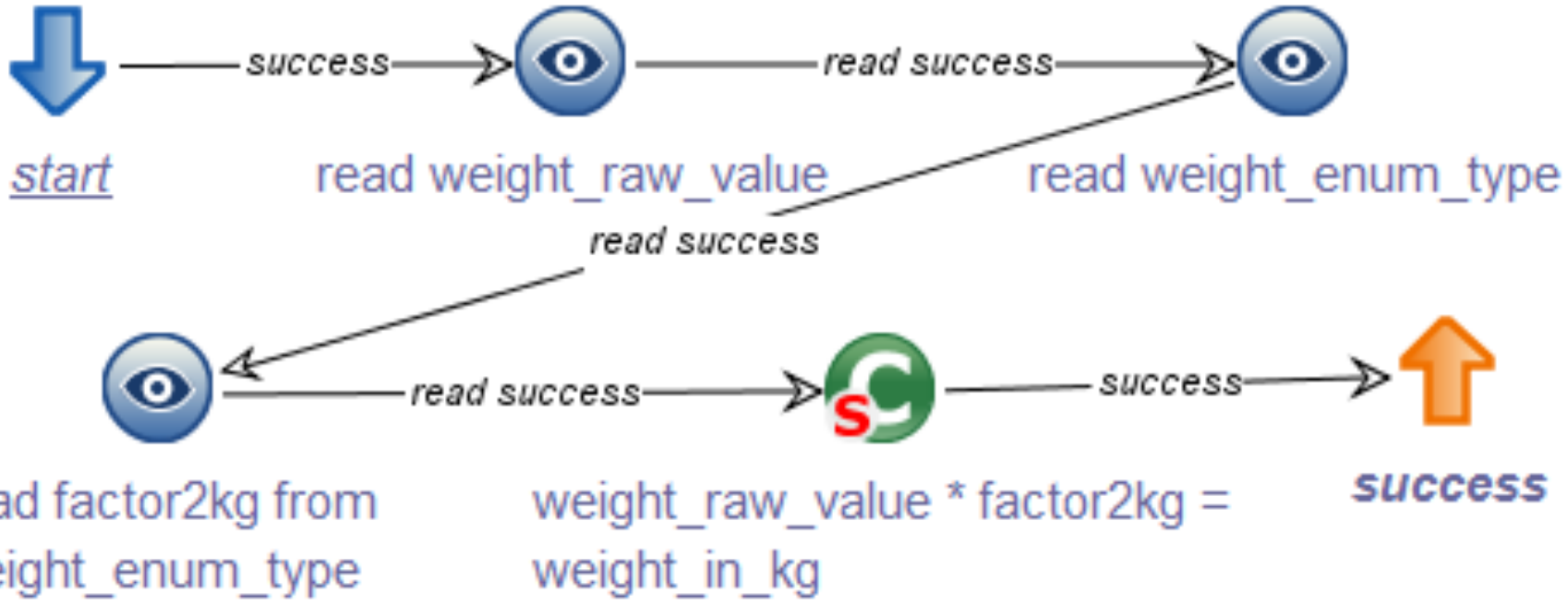
# Process Models: Kripke Transition System (KTS)



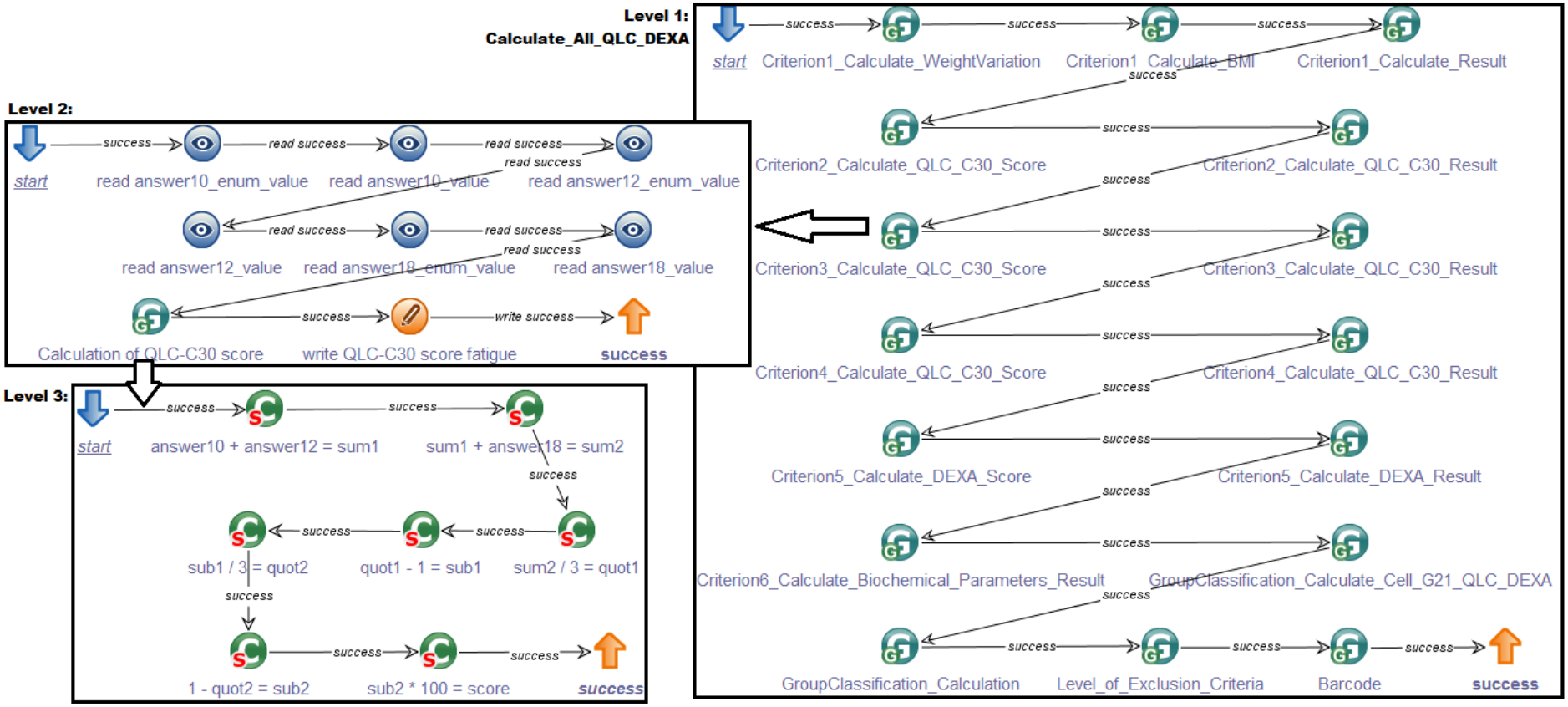

Let *AP* be a set of atomic propositions.
A **Kripke Transition System** over *AP is a 4-tuple* *K*=(*S,Act Trans,I*) with:

| | |
|---|---|
| $S$ | a set of states |
| $Act$ | a set of actions |
| $Trans \subseteq S \times Act \times S$ | a transition relation |
| $I : S \rightarrow 2^{AP}$ | an interpretation function |

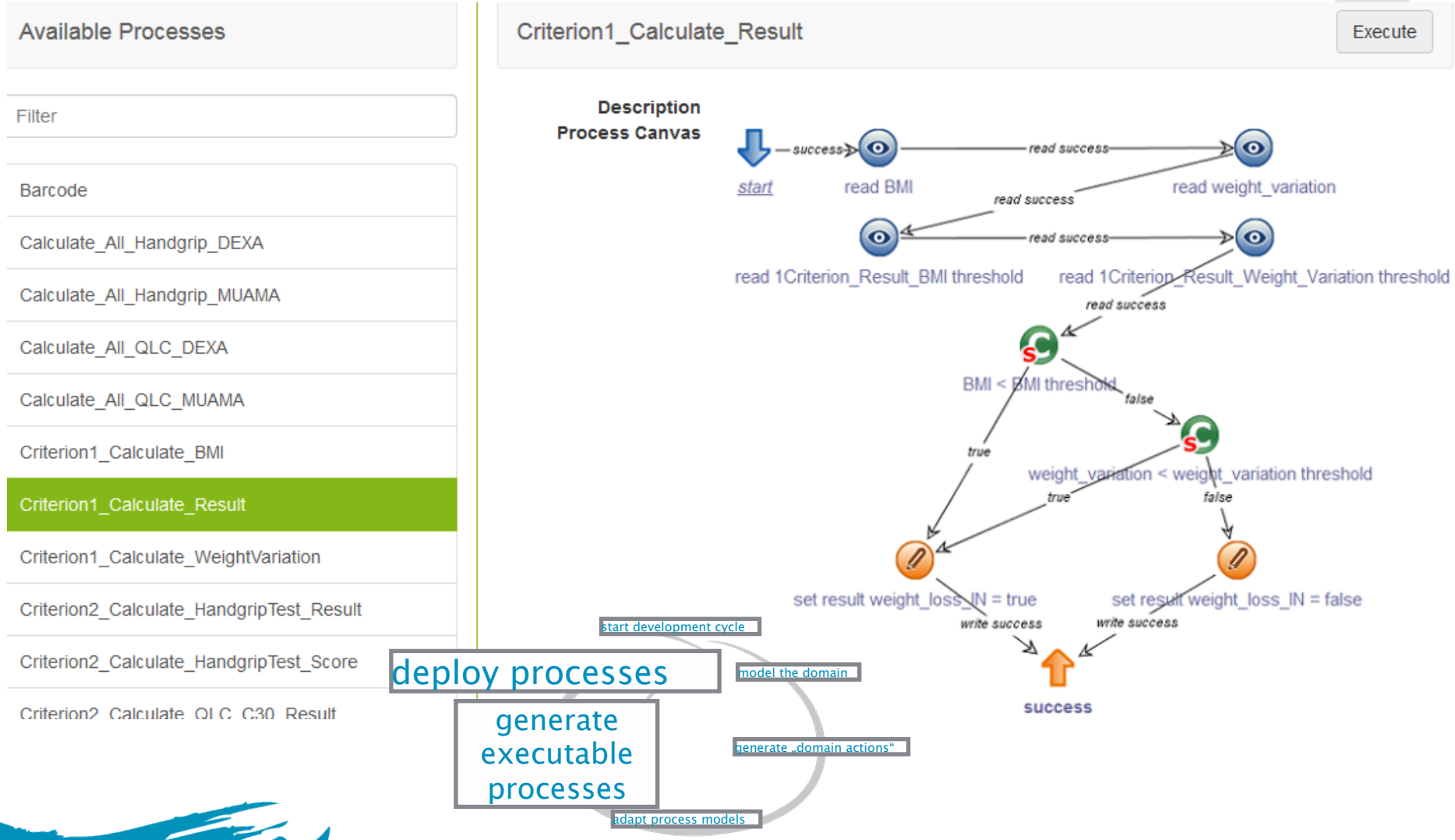
# Process Model: TransformWeight2kg

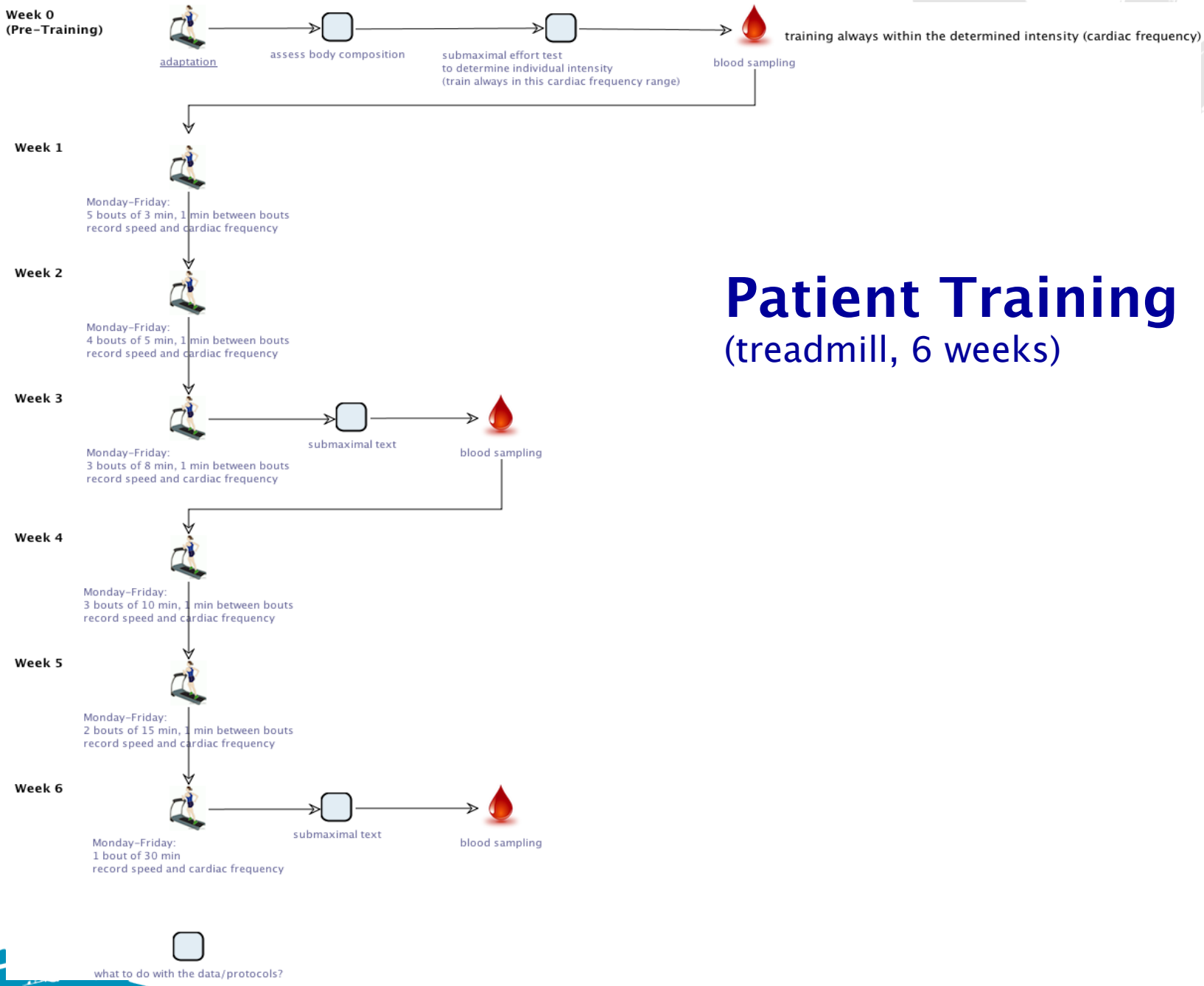


# Path through Graph Level Hierarchy



# Executable Processes deployed to DyWA

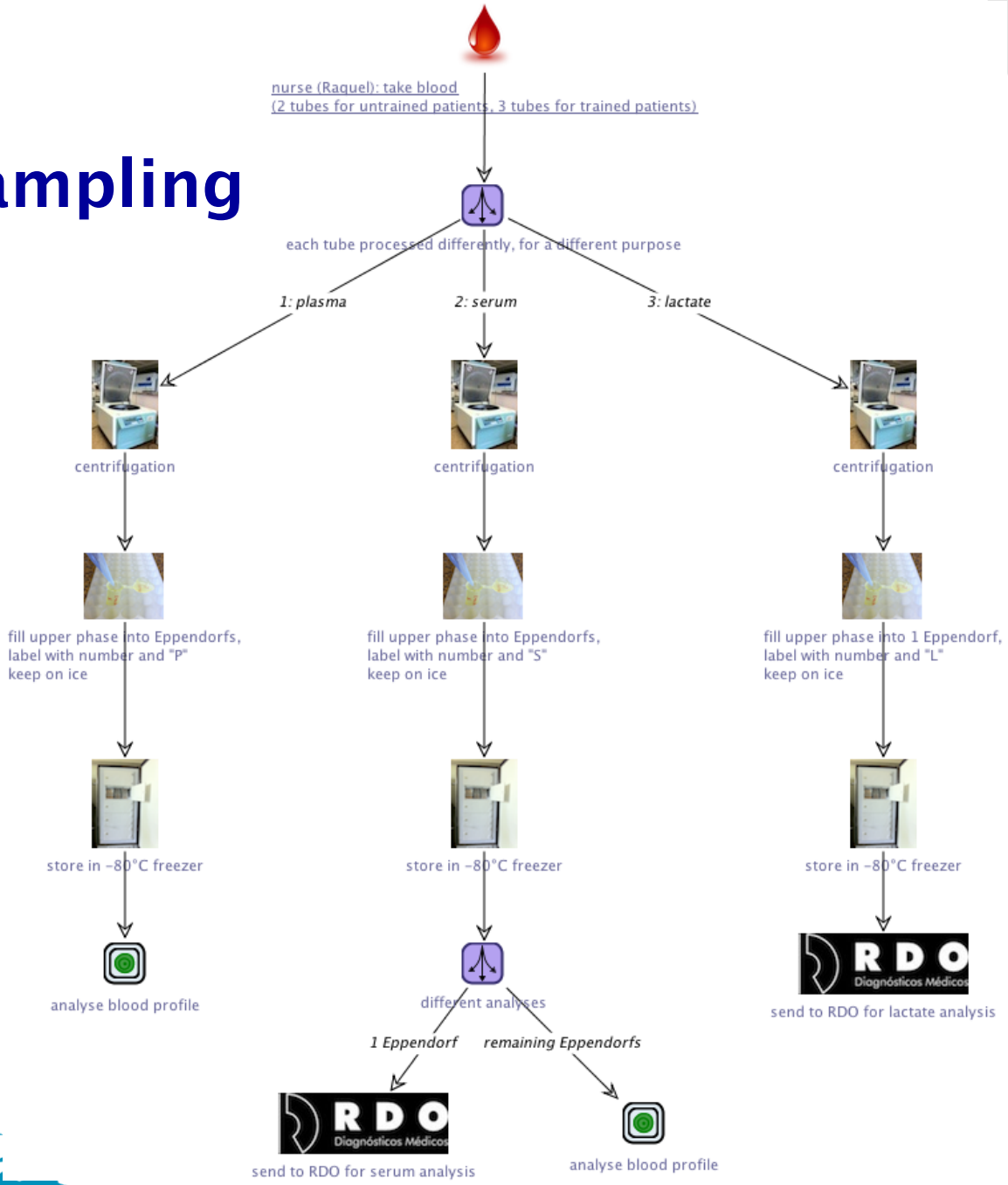





# Patient Training

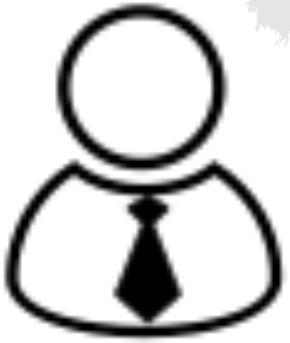
(treadmill, 6 weeks)

# Blood sampling



# Outcome:
# Incremental Modeling of Data and Processes

| Group | Institute/Country |
|---|---|
| Alessandro Laviano,<br>Maurizio Muscaritoli | Department of Clinical Medicine<br>Sapienza University of Rome,<br>Rome, Italy. |
| Giorgio Trinchieri,<br>Romina Goldszmid | Center for Cancer Research<br>National Cancer Institute,<br>Bethesda, Maryland USA |
| Josep M. Argilés,<br>Silvia Busquets | Cancer Research Group,<br>Institut de Biomedicina, Univ. Barcelona<br>Barcelona, Spain |
| Nicolaas Deutz | Department of Health & Kinesiology<br>Texas A&M University<br>Bryan, Texas, USA |
| Stephen Farmer | Department of Biochemistry<br>Boston University School of Medicine<br>Boston, MA, USA |
| Gerhard Paul Püschel | Institute of Nutritional Science<br>University of Potsdam<br>Potsdam, Germany |
| *Tiziana Margaria* | *Institute of Informatics*<br>*University of Potsdam*<br>*Potsdam, Germany* |
| *Barry D. Floyd* | *California State Polytechnic University*<br>*San Luis Obispo, CA, USA* |



Application Experts

Technical Experts

# Outcome:
# Incremental Modeling of Data and Processes

- patient classification process is now fully automated as a workflow
  - modeled with jABC4, and
  - integrated into a database provided by the DyWA
- **jABC4** = model-driven environment for designing the processes
- **DyWA** = meta-schema based data definition and management tool with standard relational database
- their interplay provides an integrated environment for **data and process modeling** along the XMDD paradigm
- supports a Service-oriented Continuous Engineering approach to the formalization and definition of a **domain-specific language** and **process landscape**

# eXtreme Model Driven Design


http://cinco.scce.info/


+


http://hope.scce.info


http://dime.scce.info/

# Limerick's vision


Thank you!

Questions?

Contact: *tiziana.margaria@lero.ie*

# Conclusion

- integrated data and process modeling environment:
  - data collection,
  - data transformation,
  - automation,
  - reproducibility of results
- many **processes** have the potential to be **reused** by other health care applications, or even in other domains

# Conclusion

- **adaptations** to changing experimental setups are still possible
- **processes** are **immediately executable** and remain customizable
- this environment provides a significant step towards the large-scale applicability of a **formal** model-based and methods-supported, model-driven, generative IDE for scientists
- the IDE ensures that the modeling of domain-specific data types **and** processes using these components happens in one coherent system at a user-accessible level
- **result**: immediate availability, consistency and reproducibility of the outcomes, and the coherence and evolvability of the entire collection of data schema and processes

# Ongoing Work

- **access to data and processes** in the web application should be based on a proper **roles and rights management** (e.g. DIME)
- **provenance tracking** and **auditing** of all the data collected and accessed
  - to know **who** did **what when** with **which permissions**, and
  - to maintain truly **complete records** of experimental results